

REMARKS/ARGUMENTS

The invention

This invention provides for an anti-allergy agent comprising a cell penetrating peptide [CPP] from Kaposi fibroblast growth factor fused to either of two specific inhibitors of mast cell activation, Gat or Gai₃. In a test of four different CPPs, the claimed CPP from Kaposi fibroblast growth factor [Seq ID No. 3] was surprisingly discovered to be the *only* CPP able to transport its inhibitor domains in a manner that **inhibited** mast cell activation.

Status of the pending claims

Claims 63-70 and 72-78 are pending. Claim 79 was canceled because it was redundant.

Examiner Interview

Pursuant to Rule 133(b), applicants acknowledge the interview of September 28, 2007, with Supervisor Christina Chan. During the interview, applicants' attorney requested clarification of the Office's position with regard to the rebuttal evidence for the *prima facie* case of obviousness. Examiner Crowder replied that the rebuttal evidence relating to unpredictability was irrelevant because the claims did not encompass the non-working combinations. Supervisor Chan agreed with Examiner Crowder's position.

The undersigned stated that this position is contrary to decisional law relating to rebuttal of a *prima facie* case of obviousness and requested that the examiner reconsider their position in view of the law provided below and to discuss the situation with their colleagues before finalizing the rejection. Supervisor Chan agreed to discuss this case with her colleagues, which is how the case presently stands.

REJECTIONS UNDER 35 U.S.C. §103

THE EXAMINER HAS SET FORTH A *PRIMA FACIE* CASE OF OBVIOUSNESS.

Holgate in view of Aridor and Lin

There is a single rejection of the independent claim 63 with the rejection of claims 64 and 65 succeeding or falling with claim 63. Applicants concede that the *prima facie* case of obviousness has been properly set forth by the combination of references.

The Examiner has rejected pending claims as obvious over Holgate in view of Aridor and Lin. Holgate is relied upon as generally teaching that pharmacological agents can inhibit mast cell degranulation and these agents are useful for treating diseases such as asthma. Aridor teaches Seq. ID No. 1 (KNNLKECGLY) and Lin teaches the Seq. ID No. 3 CPP (AAVALLPAVLLALLAP). The Examiner presents the *prima facie* case of obviousness by arguing that she has identified the salient elements of the claims, a motivation to combine the elements, and a reasonable expectation that once combined, the recited elements would function to inhibit histamine release by mast cells.

In response, applicants presented rebuttal evidence to traverse the *prima facie* case of obviousness by surprising evidence. This evidence was considered irrelevant.

THE REBUTTAL EVIDENCE

The applicants tested several different cargo penetrating peptides for their ability to direct two mast cell inhibitors into their target mast cells. A third laboratory tried a fourth cargo penetrating peptide with one of the two mast inhibitors. A table of results and two Rule 132 declarations were presented as evidence of surprising results. In brief, only one cargo penetrating peptide proved successful at both internalizing the two inhibitors and allowing the inhibitors to function as expected. The declarants explain that the science of using cargo penetrating peptides is predictable with regard to internalization or transport of cargo into a cell; but, the functionality of the cargo once delivered is not predictable — at least not for the two claimed mast cell inhibitors.

Although the Examiner Crowder has changed her position, she initially recognized the unpredictability of the field. She wrote in the Office Action mailed August 2, 2006:

The state of the art of cell penetrating peptides can be unpredictable due to limited knowledge of the mechanism associated with mast cell exocytosis [page 4].

In finding the rebuttal evidence irrelevant, the Examiner argues that she can ignore teachings and findings of unpredictability with other cargo penetrating peptides because the claims recite only the KFGF CPP. She writes on page 5 of the outstanding Office Action:

...it is noted that the data presented on said Table regarding CPPs that are not being claimed is appear to be irrelevant in the instant application because the instant claims are drawn to methods of inhibiting mast cell degranulation using the KFGF peptide...

Therefore, the human integrin $\beta 3$ (Hu Int) and Kaposi fibroblast growth factor (KFPF), a *Drosophila* transcription factor (Dros) and transportan 10 (TP-10)... appear to be not relevant because they are not being claimed.

The Examiner then goes on to say the pending claims are irrebuttably obvious because the combination as claimed was expected to work and in fact did work. She writes on page 6:

In fact, applicant's own data appears to further demonstrate what has been taught by Lin...

Below, applicants will explain that it is not proper for the Examiner to ignore the rebuttal evidence and only focus on the evidence that supports her *prima facie* case of obviousness.

THE REBUTTAL EVIDENCE IS RELEVANT TO THE *PRIMA FACIE* CASE OF OBVIOUSNESS

The Examiner's position relies on her characterization of the rebuttal evidence as irrelevant. The fact that the field of cell penetrating peptides is unpredictable with regard to functionality of the transported peptides is not irrelevant. The failure of three other cargo penetrating peptides to deliver a functional mast cell inhibitor is decidedly relevant as comparative evidence and must be considered by the examiner. As the Federal Circuit stated in *In re Soni*:

Consistent with the rule that all evidence of nonobviousness **must** be considered when assessing patentability, the PTO **must** consider comparative data in the specification in determining whether the claimed invention provides unexpected results. 34 USPQ 2d 1684 at 1687 [emphasis added].

In re Soni and the line of cases that it arises from are controlling for the obviousness rejection of the pending claims. While the Examiner may consider and ultimately decide that comparative data does not rebut a *prima facie* case of obviousness and provide a basis for such a decision (not the case here), she cannot simply state that the comparative data is irrelevant because it is not included in the claims. In terms of formal logic, the Examiner's position is known as an "irrelevant truth." This is because whether or not applicants include comparative data in claims has no bearing whatsoever on the relevance of that data to the question being addressed.

Relevancy in law relates to the materiality of evidence in supporting or rebutting a position relating to a legal question. When a fact is *material*, it has an effect on the answer to the question at hand and it is, therefore, probative.

In our situation, the Examiner has confused the evidence **setting forth** the *prima facie* case of obviousness with evidence **rebutting** the *prima facie* case of obviousness. It is a subtle, but legally important difference. Lin (KPPF CCP) and Aridor (Gai₃) set forth the *prima facie* case of obviousness. The applicants' work with the other two CPPs and Jones' work with

the third CPP are relevant, comparative evidence because they are *material* evidence of unpredictability in the art of cell penetrating peptides.

The comparative evidence presented by applicants is material to the question of obviousness because if the CPP field is unpredictable with regard to the two claimed mast cell inhibitors, the *prima facie* case of obviousness can be rebutted and claims will be allowed.

The Examiner believes that the fact that the three other CPPs are not claimed makes them irrelevant. As stated above, this logic is flawed. The mere fact that the rebuttal evidence relates to unclaimed, non-working embodiments does not detract from its relevance in any manner. Rebuttal evidence often involves experimental evidence using non-working or less desirable combinations. For example, many pharmaceutical inventions result from painstaking comparative studies where structurally similar compounds do not exhibit the same exciting results as the claimed compounds. If the Examiner's position were correct, one could never rebut a *prima facie* case of obviousness with comparative evidence because the rejected claims never include the non-working compounds. Examples of case law involving unclaimed comparative data are easily found. Here are three examples.

In re Soni, 34 USPQ2d 1684 (Fed Cir 1995) – claiming an organic polymer with a MW of 150 KDa and comparing the claimed polymer with smaller polymers for increased tensile strength.

In re Margolis, 228 USPQ 191 (Fed Cir 1986) – claiming a method for roasting coffee in the absence of oxygen where the USPTO erred in not considering evidence in the specification that omitting oxygen makes for a better roasted coffee.

Ex parte Ohsaka, 2 USPQ2d 1463 (Fed Cir 1986) – claiming a method for making a fluoro-substituted benzene using an α -aluminum fluoride where the USPTO erred in not considering applicants' comparative data using β -aluminum fluoride.

In none of these cases did the rejected claims embrace the less preferred features of the comparative data. In *Soni*, no claim recited polymers of less than 150 kDa. In *Margolis*, no claim recited coffee roasted in the presence of oxygen. In *Ohsaka*, no claim recited β -aluminum

fluoride. Yet in all three cases, the comparative data was unquestionably relevant to the obviousness rejection.

As explained above, applicants failure to include the non-working cell penetrating cargo peptides of the comparative experiments does not render that comparative data irrelevant. You can't claim what doesn't work *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed. Cir. 2003).

RELEVANT REBUTTAL EVIDENCE MUST BE CONSIDERED AND THE PRIMA FACIE CASE OF OBVIOUSNESS WEIGHED ANEW.

Having explained that the underlying rationale for declaring the rebuttal evidence irrelevant is wrong, applicants remind the examiner that she must now weigh the facts anew. See *In re Rinehart*, 189 USPQ 143 (CCPA 1976) where the CCPA stated:

When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. Though the burden of going forward to rebut the prima facie case remains with the applicant, the question of whether that burden has been successfully carried requires that the entire path to decision be retraced. An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability.

Finally, the Examiner is reminded that she cannot simply ignore results that teach away from her position without providing scientific justification for not considering such teachings. See *Akzo N.V. v USITC*, 1 USPQ 2d 1240 at 1246 (CAFC 1986).

Having explained that the comparative data is relevant and must be considered, applicants ask that such consideration be undertaken. Applicants submit that the failure to consider the comparative data because it is irrelevant is legally baseless. Applicants remind the Examiner that Supervisor Chan had agreed to reconsider her position after the above legal arguments were presented and that she further agreed to speak with her colleagues regarding this

point of law. It is hoped that applicants can avoid unnecessary legal expenses associated with an Appeal presenting this issue to the Board.

Dependent claims 64 and 65.

Applicants rely on the above remarks and previous statements with regard to these two claims.

Double patenting

Applicants rely on the remarks previously submitted and acknowledged in the outstanding Office Action.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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